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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER

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DAVIS, M

ART UNIT

PAPER NUMBER

1642

7

DATE MAILED:

12/08/99

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 9/13/99

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s) or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

Claim(s) i- 23, 42-47, 44-45-3 is/are pending in the application.

Of the above, claim(s) 2, 8, 18-19, 48-53 is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1, 2, 4-7, 9-12, 22-23, 42-47 is/are rejected.

Claim(s) 13, 17 is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

Notice of Reference Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 13

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

Art Unit: 1642

Applicant's election with traverse of species microcapsule, endocrine cells that produce insulin, and cells that are not genetically engineered in Paper No. 6 is acknowledged. The traversal is on the ground(s) that a search directed to the independent claim would uncover any art relating to the alleged species. This is not found persuasive because the searches for the species are not co-extensive, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1, 2, 4-7, 9-17, 20-23, 43-47, species microcapsule, endocrine cells that produce insulin, and cells that are not genetically engineered. Claims 3, 8, 18-19, 48-53 are not examined because they are drawn to non-elected claims, i.e. claim 3, drawn to a hollow fiber, a disc or a sphere; claim 8, drawn to transplanted genetically engineered cells; claims 18-19, drawn to neuroectodermal cells; and claims 48-53, drawn to a method of inhibiting graft rejection, using a substance, CTLA4Ig, which inhibits the immune-system costimulation, without altering the cytokine profile of the subject, i.e. via encapsulated engineered cells that produce CTLA4Ig.

### **CLAIM OBJECTION**

Claims 13, 17 are objected to because claims 13, 17 are Markush claims, which are not properly written.

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### **REJECTION UNDER 35 USC 112, SECOND PARAGRAPH**

Art Unit:

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is indefinite because it is not clear whether the language ...inhibiting...activated macrophages "capable of" reacting with the viable cells... means ...inhibiting....macrophages "from" reacting with the viable cells... or ....inhibiting the activation of macrophages, which is capable of reacting with the viable cells...

### **REJECTION UNDER 35 USC 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit:

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-7, 9-17, 20-23, 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lenschow, DJ et al, 1992, Science, 257: 789-792, in view of Goosen et al, PN=4,673,566, Soon-Shiong P et al, 1990, Horm Metab Res Suppl, 25: 215-9, Akalin, E et al, 1996, Transplantation, 62(12): 1942-5, Linsley, PS, et al, 1994, EP 0 613 944, Padrid PA et al, 1998, Am J Respir Cell Mol Biol, 18(4): 453-62, Steurer, W et al, 1995, J. Immunol, 155(3): 1165-74.

Claims 1, 2, 4-7, 9-17, 20-23, 43-47 are drawn to a method for preventing graft rejection of transplanted insulin-producing cells, by 1) prior to transplantation, containing grafted cells in a microcapsule, and 2) administering soluble CTLA4Ig, which inhibits the production of immunoglobulins, and the activation of macrophages, and which increases the production of gamma-interferon and binds to complement. The microcapsule is impermeable to immunoglobulin and/or lymphocytes.

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Lenschow et al teach CTLA4Ig blocks human pancreatic islet rejection in mice by affecting T cell recognition of B7+ antigen-presenting cells.

Lenschow et al do not teach encapsulation of transplanted cells in a microcapsule which is impermeable to immunoglobulin and/or lymphocytes. Lenschow et al do not teach that CTLA4Ig inhibits the production of immunoglobulins, and the activation of macrophages, and that CTLA4Ig increases the production of gamma-interferon and binds to complement.

Goosen et al teach microencapsulation of transplanted islets of Langerhans in a semipermeable microcapsule, which is impermeable to immune system proteins. Said microcapsule has a molecular weight cut off of below about 150,000 dalton, and has a controlled thickness of polylysine.

Soon-Shiong et al teach that microencapsulation of isolated islets prevents graft rejection, by protecting the transplanted cells from both cytotoxic T-lymphocytes and natural killer cells.

Akalin et al teach that CTLA4Ig inhibits cell-mediated and humoral immune response, and prevents macrophage activation and infiltration into the graft site.

Linsley et al teach that CTLA4Ig inhibits immunoglobulin secretion (p.19).

Padrid et al teach that interferon-gamma in CTLA4Ig-treated mice increases significantly as compared to the untreated animal.

Steurer et al teach that because of the mutation in the C'1q binding sites of the Fc portion of CTLA4Ig, CTLA4Ig binds to, but does not target, cells for complement-directed cytolysis (abstract).

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The art establishes that it was possible at the time the invention was made to block human pancreatic islet rejection in mice using CTLA4Ig, which affects T cell recognition of B7+ antigen-presenting cells. The art further teaches that graft rejection of transplanted islet cells could be prevented by microencapsulation of islet cells, wherein by a molecular weight cut off at about 150,000 daltons, the semipermeable membrane does not allow cytotoxic T-lymphocytes and natural killer cells to reach the grafted cells, thus preventing the graft rejection. The art also teaches that CTLA4Ig inhibits the production of immunoglobulins, and the activation of macrophages, and that CTLA4Ig increases the production of gamma-interferon and binds to complement.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to block human pancreatic islet rejection in mice using CTLA4Ig, which affects T cell recognition of B7+ antigen-presenting cells, as taught by Lenschow et al. It would have been obvious to encapsulate the grafted cells, which is treated with CTLA4Ig, as taught by Goosen et al and Soon-Shiong et al, because the encapsulation also prevents graft rejection, but by a different mechanism, thus by logical reasoning, would increase the chance of preventing graft rejection by the immune system. It would have been obvious to use microcapsules that are impermeable to cytotoxic T-lymphocytes and natural killer cells to reach the grafted cells, for preventing the graft rejection by said immune-system, as taught by Goosen et al and Soon-Shiong et al. One of ordinary skill in the art would have been expected that CTLA4Ig inhibits the production of immunoglobulins, and the activation of macrophages, and

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that CTLA4Ig increases the production of gamma-interferon and binds to complement, because they are inherent properties of CTLA4Ig, as taught by Akalin et al, Linsley et al, Padrid et al, and Steurer et al. One of ordinary skill in the art would have been motivated to block encapsulated pancreatic islet rejection using CTLA4Ig, with a reasonable expectation of success. The motivation is obvious, i.e. to prevent graft rejection of islet cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 10:00 am to 2:00 pm, except on Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-4227.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [Paula.Hutzell@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set

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forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

November 4, 1999



PAULA K. HUTZELL  
SUPERVISORY PATENT EXAMINER